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Docket No.: 218025US34PCT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

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ATTORNEYS AT LAW

RE: Application Serial No.: 09/125,022

Applicants: Silvio DE FLORA, et al.

Filing Date: August 11, 1998

For: PHARMACEUTICAL COMPOSITION ENABLING
TO INHIBIT CANCER METASTASIS FORMATION
CONTAINING N-ACETYL-CYSTEINE AND
DOXORUBICIN

Group Art Unit: 1623

Examiner: Howard V. Owens, Jr.

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MAY 05 2003

TECH CENTER 1600/2900

SIR:

Attached hereto for filing are the following papers:

Request for Reconsideration (11 pp.)

Information Disclosure Statement

PTO-1449

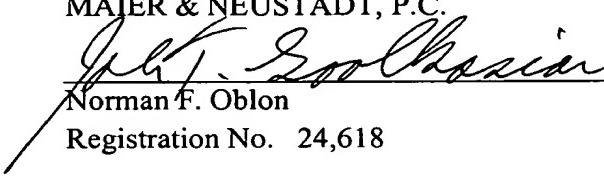
Cited References (6)

Petition for Extension of Time (one month)

Our check in the amount of **\$290.00** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R. 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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218025US34PCT



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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:

DE FLORA, ET AL. : EXAMINER: HOWARD V. OWENS, JR.

SERIAL NO: 09/125,022 :

FILED: November 24, 1998 : GROUP ART UNIT: 1623

FOR: PHARMACEUTICAL COMPOSITION ENABLING TO INHIBIT CANCER
METASTASIS FORMATION CONTAINING N-ACETYL-CYSTEINE AND
DOXORUBICIN

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REQUEST FOR RECONSIDERATION

MAY 05 2003

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

TECH CENTER 1600/2900

SIR:

Applicants hereby request reconsideration of the rejection set forth in the Examiner's Office Action mailed December 31, 2002.

At the outset, Applicants acknowledge with appreciation the Examiner's withdrawal of the finality of the previous rejection subsequent to Applicants filing of an Appeal Brief.

Applicants also note that the Office Action deals only with Claims 13-15. However, Applicants' Amendment filed March 19, 2002 included new Claims 16 and 17. The Examiner's Office Action does not refer to Claims 16 and 17. It is believed that Claims 16 and 17 were meant to be included in the Examiner's Rejection and, accordingly, Applicants have treated the Rejection as if it included Claims 13-17 rather than the stated Claims 13-15.

Claims 13-17 stand rejected under 35 U.S.C. 102(b) as being anticipated by either Freeman et al. ("Freeman"), *Toxicology and Applied Pharmacology*, Vol. 54, pp. 168-175 or

Doroshow et al. ("Doroshow"), *J. Clinical Investigation*, Vol. 68, pp. 1053-64. This rejection is respectfully traverse.

The Examiner has noted the language of the claims recites a process wherein treatment is conducted on a patient having a tumor that "has not yet metastasized, but is capable of metastasizing." However, it is noted that the claims also include other limitations. In this case, the patient to whom the pharmaceutical is administered must have a "primary cancerous tumor." Normally, such a tumor would be a naturally occurring tumor since one does not ordinarily transfer a tumor to a "patient" when that patient is a human.

The Examiner has noted that Freeman and Doroshow "inherently" achieve the prevention of metastasis. However, the Examiner has provided no proof of this. Rather, the Examiner is using Applicants' disclosure against them. As noted by the court in *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323 (CCPA 1981), the mere fact that a certain thing may result from a given set of circumstances is not sufficient to prove inherency. Inherency may not be established by probabilities or possibilities. Something that is inherent must inevitably be the result each and every time.

It is by now well settled that the burden of establishing a *prima facie* case of anticipation resides with the Patent and Trademark Office. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), quoting *In re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967).

As noted by the Board of Patent Appeals and Interferences in *Ex parte Skinner*, 2 USPQ2d 1788, before an Examiner can switch the burden of proof of showing non-inherency to the applicant, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art. In this case, the Examiner has provided no such evidence.

It is Applicants' position that the experimental models used by Freeman and Doroshow are simply not suitable for the study of metastasis, and there is no evidence that metastasis would have occurred during the Freeman and Doroshow testing program. Both Freeman and Doroshow use murine models of tumors which produce ascites in the peritoneal cavity. These tumors were obtained by transplanting the ascites fluid from mice in which the tumor was maintained to non-tumorous mice that received, directly into the peritoneum, either Ehrlich ascites cells (Freeman) or P388 leukemia cells (Doroshow). These experimental mice are "models" of primary tumors growing in the peritoneal cavity. These "models" are not suitable for the study of metastasis largely because both tumors are rapidly fatal to mice. The Examiner's attention is directed to the Freeman reference, Table 1, which shows that in the absence of adriamycin (doxorubicin) or N-acetyl-cysteine treatment, the life span of the mice implanted with Ehrlich ascites tumor ranged between 14 and 22 days. Similarly, the survival time of the Doroshow mice, absent treatment, was only 8 days. (*See Fig. 2 of Doroshow*). In other words, the models used by both Freeman and Doroshow were models of primary tumors and were incapable of determining the effect of the treatment on metastasis.

The Examiner's attention is also directed to U.S. Patent No. 4,331,648 to inventors Myers, Doroshow and Locker, three of the authors of the Doroshow article. The patent includes a section regarding anti-tumor effectiveness which describes the work of Doroshow in layman's terms. It is stated therein that the experiments with P388 ascites tumor cells demonstrate that N-acetyl-cysteine does not in and of itself possess anti-tumor properties and does not interfere with doxorubicin's ability to treat the sensitive P388 ascites tumor. (Col. 3, lines 30-52). The P388 tumor used is described by Doroshow as one which is "one of the most sensitive of the murine tumors to doxorubicin (adriamycin)." ('648 patent, col. 3, lines 31-32).

It should be noted that Applicants' work on the metastatic phase of cancer used a different, more appropriate model, i.e., B16-F10 melanoma cells. Indeed, Applicants' work was published in 1996 in the *Int. J. Cancer*, 67, 842-848 (1996), a "peer review" journal. Accordingly, Applicants' work, which used appropriate models, is highly respected as judged by Applicants' peers.

In an effort to understand and better explain to the examiner the appropriateness of the "model" used by Applicants for determining metastasis (as opposed to the inappropriate Freeman and Doroshow "models"), Applicants' attorney requested his librarian to perform a literature search using keywords such as "model" and "metastasis" to uncover prior art which could shed some light on why metastases would not be expected in the models used by Freeman and Doroshow. The following information obtained from the search is sufficient to show a lack of inherency in the Freeman and Doroshow protocols. Copies of the references are included in an IDS filed herewith.

(a) Birt, "Methodologic Issues, Theoretical Considerations, and Design Criteria for Experimental Animal and Cell Culture Experiments," *Am J Clin Nutr* 1997;66 (Suppl): 1506S-12S (1997). This reference provides an interesting and easily understood discussion regarding animal models of cancer. At p. 1509S, Birt states:

Considerations in selection of cell lines for transplantation studies include whether the cells are competent for metastasis and can progress to metastasis when put into the host or whether they will form a large tumor that will kill the host before metastasis can occur. An ideal model would allow implanted cells to grow into a tumor that then would metastasize in a permissive environment. . . .

Cell lines that can form metastases on injection into an appropriate host can be used as experimental metastasis models. Cells are injected intravenously and seed in the lung or other appropriate sites. Metastases can be counted on the surface of the lung. . . .

Another consideration in designing animal models to mimic cancer progression to metastasis is deciding where the tumor cells will be placed in the animal model. It would appear logical to put the cells in the site of the primary tumor (autologous transplantation). This approach has been successful in several models (e.g., for

breast, prostate and colon cancer). However, autologous transplantation may lead to rapid rejection of cells. Oftentimes the only site where the cells can form a tumor that will eventually metastasize is in a fat pad, under the kidney capsule, or intradermally, sites that protect the growing cells from lymphocyte surveillance. (Emphasis added.)

(b) Budzynski, "Lewis Lung Carcinoma in Mice as an Experimental Therapy

Model, I. The Growth Kinetics and the Effect of Tumor on Host," *Archivum Immunologiae et Therapiae Experimentalis*, 1982, 30, 363-372, makes the following statements:

Transplantable mouse tumors are nowadays the best but still not ideal screening system used both in evaluation of new anti-cancer drugs and in programming of different treatment strategies. Majority of anticancer drugs used presently in clinic were selected in mice bearing L1210 and P388 leukemias. These are exponentially, fast growing tumors with high proliferating fraction, which kill the host within few days.

Drugs already selected by these models appeared to be effective in the treatment of patients mostly with leukemias and lymphomas. On the other hand, the solid tumors like e.g., lung cancer, gastrointestinal cancer are in majority of cases resistant to the treatment. Thus, the great interest is focused on the slow growing solid mouse tumors as the screening models which could substitute [for] the transplantable mouse leukemias in the selection of anticancer drugs active in human solid tumors. Such animal models include: Lewis lung carcinoma, B16 melanocarcinoma . . . (Emphasis added.)

It should be noted that the B16 melanocarcinoma mentioned by Budzynski is the solid tumor model used by Applicants in their work on metastasis. Interestingly, Budzynski utilized Lewis lung carcinoma which he discovered metastasized to the lungs. This carcinoma required eight days to form micrometastases and 16 days to form macrometastases after tumor cell implantation. (p. 366). It should also be noted that the survival time of the mice ranged from 19 through 60 days depending upon the number of cells used in the inoculum. Moreover, the tumor cells were not inoculated in the intraperitoneal cavity as were the cells of Freeman and Doroshow.

(c) Futakuchi et al., "Establishment of an *In Vivo* Highly Metastatic Rat

Hepatocellular Carcinoma Model," *Jpn. J. Cancer Res.*, **90**, 1196-1202, November 1999.

Futakuchi appears to have worked with induction of liver carcinomas which have a tendency

to metastasize to the lungs. The author notes that an increase in body weight characteristic of metastasis occurred from about 8 to 22 weeks after cancers were induced. The first mortalities were said to be observed in week 16. The animals died as a result of massive bleeding from either primary HCCs in the liver or metastatic nodules in the lung. Again, the reference appears to show that development of metastases takes time and that experimentation for metastasis requires a model different from that used by Doroshow and Freeman.

(d) McGarvey et al., "The Effect of Butyric Acid and Retinoic Acid on Invasion and Experimental Metastasis of Murine Melanoma Cells," *Clin. Expl. Metastasis*, 1990, Vol. 8, No. 5, 433-448, discusses *in vivo* models for metastasis. One model used was tail vein injection of tumor cells. The cells were described as B16a cells, essentially the same model used by Applicants in doing their work with the exception that the Applicants injected the melanoma cells into the foot pad, an acceptable alternative for the tail vein.

From the above references it can be seen that the "models" used by Freeman and Doroshow were not chosen to demonstrate metastasis and not suitable for metastasis prevention studies. This is understandable because the work done by Freeman and Doroshow was designed to determine whether or not N-acetyl-cysteine would protect against cardiac arrest that was caused by adriamycin. As part of that experiment, the authors noted that the N-acetyl-cysteine did not adversely affect the anti-tumor characteristics of the doxorubicin. No beneficial effect on anti-tumor characteristics was noted.

Our literature search also uncovered a reference describing work conducted in 1986 involving the administration of methotrexate and adriamycin (doxorubicin) to treat cell bladder carcinoma. The reference, Drago et al., "Nb Rat Transitional Cell Bladder Carcinoma Model: Dose Response to Methotrexate and Adriamycin," *Anticancer Research* 6: 1019-1020 (1986), describes work conducted with a tumor model transplanted into the

right flank of suitable Nb rat hosts. The authors administered methotrexate in two doses and adriamycin in two doses. (2.5 mg. and 5 mg/kg). The author advises that methotrexate at a dose of 5.0 mg/kg, reduced the tumor volume and that only one of the nine animals had metastatic disease. Adriamycin at the same dose was more successful in terms of reduction of tumor volume and metastasis. However, four of the nine animals tested died because of myocardial problems and pulmonary congestion. The reference states that the mortality rate of 50% was "unacceptable." A lower dosage of 2.5 mg/kg resulted in only one animal in the group having metastatic disease as well as the tumor volume being significantly reduced.

It is respectfully submitted that the Drago reference actually teaches away from utilizing adriamycin at relatively high effective dose, i.e., 5.0 mg/kg. Moreover, it does not suggest improving the metastatic effect of adriamycin by co-administering N-acetyl cysteine. Applicants, on the other hand, were able to utilize doxorubicin at a much higher dose, i.e., 10 mg/kg body weight. Moreover, Applicants utilized doxorubicin in conjunction with NAC to synergistically enhance the inhibition of metastasis, an effect not contemplated by Drago. Applicant's discovery of enhanced inhibition of metastasis is completely contrary to the Freeman and Doroshow work, both of which suggested that NAC has essentially no effect on the anti-tumor activity of doxorubicin. *See*, in particular Doroshow et al., *J. Clin. Invest.*, p. 1060, col. 1 (the entire column under the figure), which concludes

These results suggest that a dose of NAC (2,000 mg/kg) that ablates electron microscopic evidence of doxorubicin cardiac toxicity **does not interfere with the drug's antitumor activity against P388 leukemia.**

When the references themselves state that NAC has no effect on the anti-tumor activity of doxorubicin, how can the Examiner maintain an unsupported "inherency" rejection?

It is clear that the model used by Freeman and Doroshow is simply not a “metastatic” model. Hence, the Freeman and Doroshow experiments could not “inherently” constitute an anticipation of the claimed subject matter.

It should be noted that to the best of Applicants’ knowledge, the combination of N-acetyl cysteine and doxorubicin has not been approved by the drug administration of any country including the United States (FDA). Accordingly, an “inherency” cannot occur as a result of legitimate actual practice. Moreover, the *Physicians Desk Reference* (PDR) notation for doxorubicin (adriamycin) acknowledges the potential cardiac problem caused by doxorubicin and does **not** suggest administering N-acetyl-cysteine to ameliorate the cardiac problems. (A copy of pertinent pages of the 2003 PDR is attached hereto.) In other words, the work of Freeman and Doroshow has not been accepted even for its teachings of preventing heart failure.

It is respectfully submitted that prevention of metastasis is **not** inherent in the testing models used by Freeman and Doroshow. It is also respectfully submitted that as evidenced by the PDR the suggestion of Freeman and Doroshow to combine adriamycin with N-acetyl-cysteine has **not** been accepted by the prior art for actual treatment, other than the models used by Freeman and Doroshow. If any alleged “inherency” occurred in the Freeman or Doroshow experiments, it was clearly non-intended, accidental and unappreciated. Accordingly, the alleged inherency (which the Examiner has not proved) cannot constitute an anticipation under the case law as pronounced by the Supreme Court of the United States in *Tilghman v. Procter*, 102 U.S. 707 (1880) and *Eibel Process, Co. v. Minnesota and Ontario Paper Co.*, 261 U.S. 45 (1923). See also *In re Felton*, 179 USPQ, 295, 298 (CCPA 1973).

As has previously been pointed out by Applicants, the invention herein is directed to a new use of an old combination of pharmaceuticals and a new use of an old process of administering the chemicals. The references relied on by the Examiner, Freeman and Doroshow, utilized doxorubicin at what was considered to be sub-lethal dosages of 1.5 or 2.5 mg/kg/day (Freeman) and 5 mg/kg doxorubicin (Doroshow) and concluded that except for its beneficial effect on the patient's heart, NAC had no effect on the tumor activity of doxorubicin. Applicants, on the other hand, were able to utilize the doxorubicin at significantly higher doses in some experiments. Applicants have discovered that the combination of doxorubicin and N-acetyl-cysteine is synergistic in preventing metastasis. *See Specification, p. 2, lines 9-19, especially lines 17-19.* Drago, who noted a metastatic effect with methotrexate and doxorubicin in some cases, did not suggest combining methotrexate or doxorubicin with N-acetyl-cysteine, as did Applicants, in order to obtain a new anti-metastatic result which is superior to that of doxorubicin alone. (Incidentally, Drago teaches that prevention of metastasis is not "inherent" because it did not always happen in his experiments.)

If one considers that it is the purpose of the patent system to promote the progress of the useful arts, Applicants' invention should be patented. The prior art in the form of Doroshow and Freeman merely noted as a conclusion that N-acetyl-cysteine does not adversely affect the anti-tumor activity of doxorubicin. The prior art in the form of Drago merely advises that at high dosage doxorubicin prevented metastasis but that the patients died from heart problems caused by the adriamycin. Applicants have combined both N-acetyl-cysteine and doxorubicin and have learned that the results regarding metastasis are synergistic, and significantly so. This work has been judged of value by a peer review journal which permitted its publication. Moreover, Applicants have defined the process in

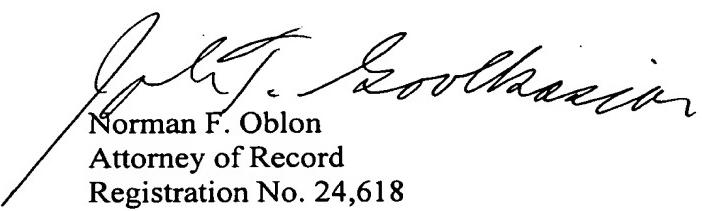
the claims such that it reads on a new use for an old composition, i.e., administration to treat tumors which are subject to metastatization, in order to prevent the formation of metastases.

The Examiner should remember that absent the benefits of the patent system, there is no incentive to develop Applicants' new use. The patent statutes and the courts recognize this and, accordingly, have made room for patents to a new use for an old composition or process. The claims at issue are directed to that new use. Inherency has not been shown or explained by the Examiner. Applicants have challenged the Examiner's unsupported assumption of inherency and have shown that inherency does not inevitably occur in the prior art processes of record. The requirements of the patent statutes permitting patents for new uses have been met.

It is respectfully submitted that the claims of this Application are in condition for allowance and an early indication of allowability is requested.

Respectfully submitted,

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